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Patentanmeldung Nr. Patent application No. Demande de brevet n°

03006059.4

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For the President of the European Patent Office

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ALLEMAGNE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Clofarabine derivatives

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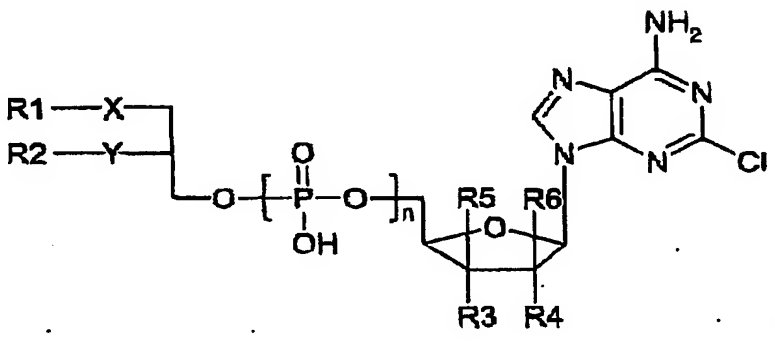
Clofarabine derivatives

The subject of the present invention are specific lipidesters of nucleotides of the general formula I,



(I)

wherein

R^1 is a straight-chain or branched, saturated or unsaturated alkyl residue having 1-20 carbon atoms, optionally mono- or polysubstituted by halogen, C_1-C_6 alkoxy, C_1-C_6 alkylmercapto, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkylsulfinyl or C_1-C_6 alkylsulfonyl groups,

R^2 is hydrogen, a straight-chain or branched, saturated or unsaturated alkyl chain having 1-20 carbon atoms, optionally mono- or polysubstituted by halogen, C_1-C_6 alkoxy, C_1-C_6 alkylmercapto, C_1-C_6 alkoxycarbonyl or C_1-C_6 alkylsulfonyl groups,

R^3 represents hydrogen, hydroxy or halogen,

R^4 represents hydroxy or hydrogen,

R^5 represents hydrogen or hydroxy,

R^6 represents a halogen,
with the proviso that at least one of the residues R^3 or R^5 is hydrogen, or R^3 and R^4 can signify a further bond between C-2' and C-3',

X represents a valence bond, oxygen, sulfur, a sulfinyl or sulfonyl group,

Y is a valence bond, an oxygen or sulfur atom, and

n is an integer of 1, 2 or 3,

their tautomers and their physiologically acceptable salts of inorganic and organic acids and bases, as well as processes for their preparation and medicaments containing these compounds as active ingredients.
The amino group in the adenine residue of the general formula I can also be protected by well known amino protecting groups.

Since the compounds of the general formula I contain asymmetric carbon atoms, all optically-active forms and racemic mixtures of these compounds are also the subject of the present invention.

J. Biol. Chem. 265, 6112 (1990) and EP-A-0,350,287 describe preparation and use of liponucleotides as anti-viral drugs. Therein, however, only dimyristoylphosphatidyl and dipalmitoylphosphatidyl residues coupled to well known nucleosides such as AZT and DDC are disclosed, including their fatty acid ester structure.

J. Med. Chem. 33, 1380, (1990) describes nucleoside conjugates of thioether lipids with cytidine diphosphate, which have antitumor activity and might find use in oncology.

Chem. Pharm. Bull. 36, 209 (1988) describes 5'-(3-sn-phosphatidyl)nucleosides having antileukemic activity, as well as their enzymatic synthesis from the corresponding nucleosides and phosphocholines in the presence of phospholipase D with transferase activity.

The patent application WO 92/03462 describes thioether lipid conjugates having antiviral activity, particularly for the treatment of HIV infections.

The synthesis of 2-Chloro-9-(2'-deoxy-2'-fluoro arabinofuranosyl)adenine (known as Clofarabine) is described in J. Org. Chem. 34, 2633 (1969) and in the patent application WO 01/60383.

The pharmacological activity of 2-Chloro-9-(2'-deoxy-2'-fluoro arabinofuranosyl)-adenine as inhibitor of DNA replication in comparison to other nucleosides is also described in Hematology 463 (1999).

Other halo arabinoadenosines with anticancer activity are mentioned in the patent applications US 5,384,310 and WO 92/20347.

The antiviral activity of such purine derivatives is shown in EP 0 314 011.

2-Chloro-9-(2'-deoxy-2'-fluoro arabinofuranosyl)adenine (Clofarabine) is a well known development product in clinical trials.
However, some toxic side effects of Clofarabine, mainly on the bone marrow, restrain the clinical use of this drug substance.

The compounds of the present invention in general formula I which incorporate the Clofarabine chemical structure, and homologues thereof, posses biological activity which distinguish them from the parent nucleosides. In particular, the compounds

of the present invention show antitumoral activity and are useful in that at pharmacological relevant doses where one or more of the toxic side effects of the parent compound is/are ameliorated and/or the covalently bound lipid part improves the bioavailability of the coupled drug substance and appears to contribute to enhanced selectivity and effectiveness of the compounds.

The compounds of the present invention have valuable pharmacological properties. In particular, they are suitable for therapy and prophylaxis of malignant tumors including, carcinomas, sarcomas, or leukemias.

Compared to the unconjugated nucleoside derivatives hitherto employed in treatment of malignant tumors, the compounds according to the invention have enhanced potency/efficacy or lower toxicity and thus, have a wider therapeutic window. In some embodiments of the present invention, the administration of pharmaceutical compositions comprising these compounds may be conducted continuously over a prolonged period of time. Incidences of withdrawal of the preparation or intermittent administration, which frequently are routine with chemotherapeutic agents due to their undesirable side-effects, may be reduced with the compounds according to this invention as compared to the parent compounds. Further, higher dose levels may be employed due to the amelioration of toxic side effects due to enhanced selectivity for tumor cytotoxicity.

The lecithin-like structure of the lipid moiety is desirable for the claimed improvements of the compounds of general formula I. The penetration through membranes and resorption barriers is facilitated and the conjugates according to formula I show a depository effect in different tissues.

The formation of lipid conjugates may also facilitate crossing the blood brain barrier due to better diffusion or active transport processes.

Similarly, the compounds of the present invention and their pharmaceutical formulations may be employed in free or fixed combination with other drugs for the treatment and prophylaxis of the diseases mentioned above.
Examples of these further drugs involve agents such as, e.g., mitosis inhibitors such as colchicines, vinblastine, alkylating cytostatic agents such as cyclophosphamide, melphalan, myleran or cis-platin, antimetabolites such as folic acid antagonists (methotrexate) and antagonists of purine and pyrimidine bases (mercaptopurine, 5-fluorouridine, cytarabine), cytostatically active antibiotics such as anthracyclines (e.g., doxorubicin, daunorubicin), hormones such as fosfestrol, taxanes, e.g. taxol, tamoxifen and other cytostatically/cytotoxically active chemotherapeutic and biologic agents.

Embodiments of the invention also encompass salts of the compounds of the general formula I, including alkali, alkaline earth and ammonium salts of the phosphate group. Examples of the alkali salts include lithium, sodium and potassium salts. Alkaline earth salts include magnesium and calcium and ammonium salts are understood to be those containing the ammonium ion, which may be substituted up to four times by alkyl residues having 1-4 carbon atoms, and/or aryl residues such as benzyl residues. In such cases, the substituents may be the same or different.

The compounds of general formula I may contain basic groups, particularly amino groups, which may be converted to acid addition salts by suitable inorganic or organic acids. To this end, possible as the acids are, in particular: hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, fumaric acid, succinic acid, tartaric acid, citric acid, lactic acid, maleic acid or methanesulfonic acid.
In general formula I, R^1 preferably represents a straight-chain C_6-C_{16} alkyl residue which may be further substituted by a C_1-C_6 alkoxy or a C_1-C_6 alkylmercapto group.

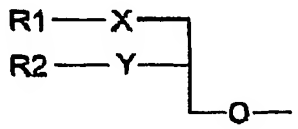
More specifically, R^1 represents a nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl or pentadecyl residue.
Preferably, methoxy, ethoxy, butoxy and hexyloxy groups are possible as substituents of R^1 residue. In case R^1 is substituted by a C_1-C_6 alkylmercapto residue, this is understood to be the methylmercapto, ethylmercapto, propylmercapto, butylmercapto and hexylmercapto residue, in particular.

Preferably, R^2 represents a straight-chain C_8-C_{15} alkyl group which may be further substituted by a C_1-C_6 alkoxy or a C_1-C_6 alkylmercapto group. More specifically, R^2 represents an octyl, nonyl, decyl, undecyl, dodecyl, tridecyl or tetradecyl group. Preferably, methoxy, ethoxy, propoxy, butoxy and hexyloxy groups are preferable as the C_1-C_6 alkoxy substituents of R^2.
In case R^2 is substituted by a C_1-C_6 alkylmercapto residue, this is understood to be the methylmercapto, ethylmercapto, propylmercapto, butylmercapto, pentylmercapto and hexylmercapto residue, in particular.

In some embodiments X is sulfur, sulfinyl or sulfonyl, and Y is oxygen.

Halogen is understood to be selected from geh group of fluorine, chlorine, bromine, iodine, wherein fluorine and chlorine are preferred.

An example of a preferred lipid moiety is the group



wherein

R^1 is $C_{12}H_{25}$

R^2 is $C_{10}H_{21}$

X is S, SO or SO_2

Y is O.

Some embodiments include compounds wherein X and Y represent a valence bond, R^2 is hydrogen, and R^1 represents a C_1-C_{20} alkyl chain optionally substituted by C_1-C_6 alkoxy or C_1-C_6 alkylmercapto.

In some embodiments, each R^3 and R^4 independently represent hydrogen or hydroxy.

In some embodiments, R^5 represents hydrogen.

In some embodiments, R^5 represents halogen, such as fluorine, chlorine or bromine, preferably fluorine.

In some preferred embodiments are compounds wherein R^3 represents a hydroxy group, R^4 and R^5 are hydrogen and R^6 is a halogen atom, such as fluorine.

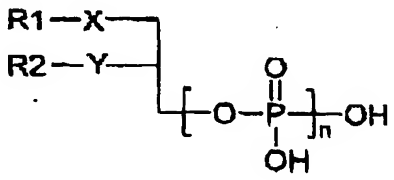
In some embodiments n is 1.

Embodiments also include compounds of the general formula I were R^3 and R^4 together represent a further bond between C-2' and C-3'.

Preferred embodiments for the nucleoside residue in the general formula I include 2-Chloro-9-(2'-deoxy-2'-fluoro arabinofuranosyl)adenine and 2-Chloro-9-(arabinofuranosyl)adenine in their protected or unprotected form.

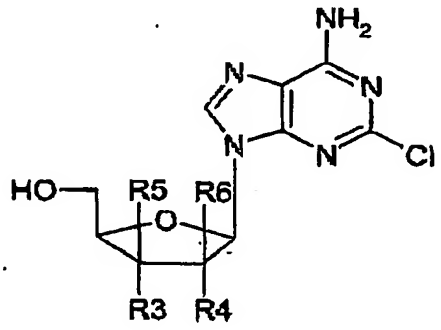
The compounds of the general formula I may be prepared by

1. reacting a compound of general formula II



(II)

wherein R^1, R^2, n, X and Y have the meaning as indicated, with a compound of general formula III



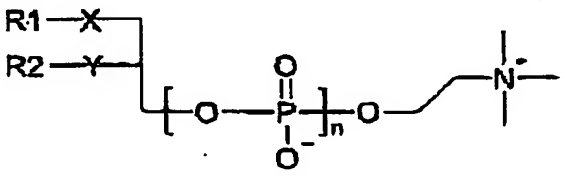
(III)

wherein R^3, R^4, R^5 and R^6 have the above-mentioned meaning, or represent a hydroxy group protected by an oxygen protecting group familiar to the artisan, in the presence of an activating acid chloride, such as 2,4,6-triisopropylbenzenesulfonic chloride, and a tertiary nitrogen base, e.g., pyridine or lutidine, in an inert solvent, such as toluene, or immediately in anhydrous pyridine, and optionally, subsequent to hydrolysis, removing the oxygen protecting groups according to procedures conventional in nucleoside chemistry,

or

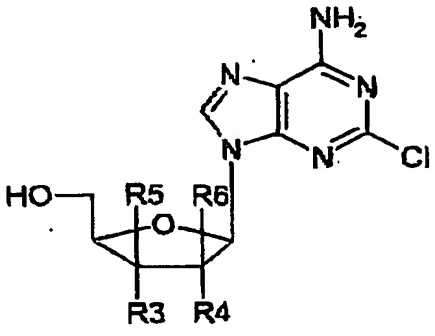
reacting a lipidalcohol (corresponding to formula II) with a nucleoside monophosphate (corresponding to formula III) in the same manner as mentioned above, or

2. reacting a compound of general formula IV,



(IV)

wherein R^1,R^2, n, X and Y have the above-mentioned meaning, with a compound of general formula III,



(III)

wherein R^3, R^4, R^5 and R^6 have the above-mentioned meaning, in the presence of phospholipase D from Streptomyces in an inert solvent, such as chloroform, in the presence of a suitable buffer, and optionally, subsequent to reaction, removing the oxygen protecting groups according to procedures conventional in nucleoside chemistry.

The preparation of the compounds of the general formula II and IV is performed in analogy to Lipids 22, 947 (1987) and J. Med. Chem. 34, 1377 (1991). Compounds of formula III are prepared in analogy to J. Org. Chem. 34, 2633 (1969) and WO 01/60383.

Salts of compounds of general formula I are prepared by reacting the free acid with alkali or alkaline earth hydroxides, alcoholates or acetates.

The "enantiomers" in the lipid parts of the compounds of formula I may be prepared by separation via diastereomeric salts or by enantioselective synthesis of the lipid residues starting with optically active C_3-precursors.

The drugs containing compounds of formula I for the treatment of cancer may be administered in liquid or solid forms on the oral or parenteral route. Common application forms are possible, such as tablets, capsules, coated tablets, syrups, solutions, or suspensions.
Preferably, water is used as the injection medium, containing additives such as stabilizers, solubilizers and buffers as are common with injection solutions. Such additives are, e.g., tartrate and citrate buffers, ethanol, complexing agents such as ethylenediaminetetraacetic acid and its non-toxic salts, high-molecular polymers such as liquid polyethylene oxide for viscosity control. Liquid vehicles for injection solution need to be sterile and are filled in ampoules, preferably.
Solid carriers are, for example, starch, lactose, mannitol, methylcellulose, talc, highly dispersed silicic acids, higher-molecular fatty acids such as stearic acid, gelatine, agar-agar, calcium phosphate, magnesium stearate, animal and plant fats, solid high-molecular polymers such as polyethylene glycol, etc. If desired, formulations suitable for oral application may include flavorings or sweeteners.
The dosage may depend on various factors such as mode of application, species, age, or individual condition.

The compounds according to the invention may suitably be administered orally or intravenously (i.v.) in amounts in the range of 0.1 – 100mg, preferably in the range of 0.2 – 80mg per kg of body weight and per day. In some dosage regimens, the daily dose is divided into 2-5 applications, with tablets having an active ingredient content in the range of 0.5 – 500mg being administered with each application.
Similarly, the tablets may have sustained release, reducing the number of applications, e.g., to 1–3 per day. The active ingredient content of sustained-release tablets may be in the range of 2-1000mg. The active ingredient may also be administered by i.v. bolus injection or continuous infusion, where amounts in the range of 5-1000mg per day are normally sufficient.

In addition to the compounds mentioned in the examples, the following compounds of formula I and their pharmacologically acceptable salts further exemplify compounds of the present invention:

1. [2-Chloro-9-(2'-deoxy-2'-fluoro arabinofuranosyl)adenine]-5'-phosphoric acid-(3-dodecylmercapto-2-decyloxy)propyl ester
2. [2-Chloro-9-(2'-deoxy-2'-fluoro arabinofuranosyl)adenine]-5'-phosphoric acid-(3-dodecylsulfinyl-2-decyloxy)propyl ester
3. [2-Chloro-9-(2'-deoxy-2'-fluoro arabinofuranosyl)adenine]-5'-phosphoric acid-(3-dodecylsulfonyl-2-decyloxy)propyl ester
4. [2-Chloro-9-(2'-deoxy-2'-fluoro arabinofuranosyl)adenine]-5'-phosphoric acid-(3-undecylmercapto-2-decyloxy)propyl ester
5. [2-Chloro-9-(2'-deoxy-2'-fluoro arabinofuranosyl)adenine]-5'-phosphoric acid-(3-undecylmercapto-2-undecyloxy)propyl ester
6. [2-Chloro-9-(2'-deoxy-2'-fluoro arabinofuranosyl)adenine]-5'-phosphoric acid-(3-decylmercapto-2-dodecyloxy)propyl ester
7. [2-Chloro-9-(2'-deoxy-2'-fluoro arabinofuranosyl)adenine]-5'-phosphoric acid-(3-dodecylmercapto-2-dodecyloxy)propyl ester

8. [2-Chloro-9-(2'-deoxy-2'-fluoro arabinofuranosyl)adenine]-5'-phosphoric acid-(3-decylmercapto-2-decyloxy)propyl ester
9. [2-Chloro-9-(2'-deoxy-2'-fluoro arabinofuranosyl)adenine]-5'-phosphoric acid-(3-undecylsulfinyl-2-decyloxy)propyl ester
10. [2-Chloro-9-(2'-deoxy-2'-fluoro arabinofuranosyl)adenine]-5'-phosphoric acid-(3-undecylsulfonyl-2-decyloxy)propyl ester
11. [2-Chloro-9-(2'-deoxy-2'-fluoro arabinofuranosyl)adenine]-5'-phosphoric acid-(3-undecylsulfinyl-2-undecyloxy)propyl ester
12. [2-Chloro-9-(2'-deoxy-2'-fluoro arabinofuranosyl)adenine]-5'-phosphoric acid-(3-undecylsulfonyl-2-undecyloxy)propyl ester
13. [2-Chloro-9-(2'-deoxy-2'-fluoro arabinofuranosyl)adenine]-5'-phosphoric acid-(3-tridecylmercapto-2-undecyloxy)propyl ester
14. [2-Chloro-9-(2'-deoxy-2'-fluoro arabinofuranosyl)adenine]-5'-phosphoric acid-(3-tridecylmercapto-2-decyloxy)propyl ester
15. [2-Chloro-9-(2'-deoxy-2'-fluoro arabinofuranosyl)adenine]-5'-phosphoric acid-(3-tridecylsulfinyl-2-decyloxy)propyl ester

EXAMPLE 1

[2-Chloro-9-(2'-deoxy-2'-fluoro arabinofuranosyl)adenine]-5'-phosphoric acid-(3-dodecylmercapto-2-decyloxy)propyl ester

0.91 g of phosphoric acid-(3-dodecylmercapto-2-decyloxy)propyl ester are treated twice with 20 ml of anhydrous pyridine and concentrated by evaporation. The residue is dissolved in 20 ml of anhydrous pyridine at room temperature, treated with 1.07 g of 2,4,6-triisopropylbenzenesulfonic chloride under nitrogen and stirred at 25°C for 0.5 hours. Then 0.5 g of 2-Chloro-9-(2'-deoxy-2'-fluoro

arabinofuranosyl)adenine (clofarabine) are added at once, and the charge is allowed to stand under nitrogen for 20 hours. Hydrolysis is performed by adding 5 ml of water, the mixture is stirred for another 0.5 hour at room temperature, freed from solvent under vacuum, and stripped twice using 50 ml of toluene. The residue is purified by column chromatography on Lichrospher 60 RPSelect B with methanol/aqueous 40mM sodium acetate 88:12 as the eluent. The product containing fractions are evaporated. The residue is distributed between 50 ml of tert.-butylmethylether and 10 ml of 2N hydrochloric acid. The organic layer is evaporated. The residue is dissolved in a mixture of 5 ml of toluene and of 5 ml of methanol. The pH is adjusted to pH 7 by addition of sodium methanolate. The solvent is stripped of and the residue is dried in vacuum.
The yield is 0.82 g (62%) white powder.

^{31}P-NMR (121,5 MHz, D_6-DMSO, 25°C): -0.4

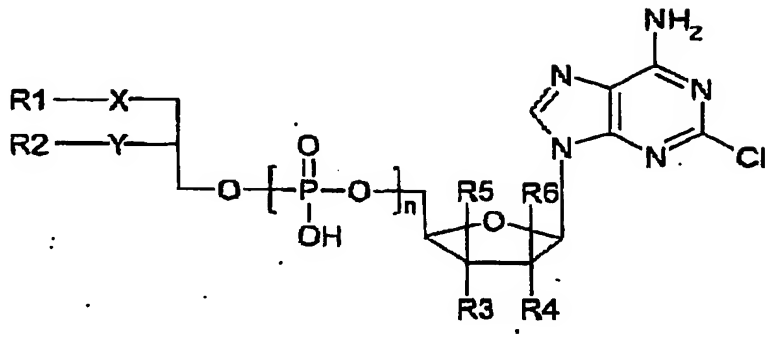
Melting point: 176°C.

The phosphoric acid-(3-dodecylmercapto-2-decyloxy)propyl ester is prepared as described in WO 92/03462.

2-Chloro-9-(2'-deoxy-2'-fluoro arabinofuranosyl)adenine is prepared according to J. Org. Chem. 34, 2633 (1969) and WO 01/60383.

Claims

1. A nucleotide derivative of formula I ..



(I)

wherein

R^1 is selected from the group consisting of a straight-chain or branched, saturated or unsaturated alkyl chain having 1-20 carbon atoms, which is unsubstituted or substituted at least once by halogen, C_1-C_6 alkoxy, C_1-C_6 alkylmercapto, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkylsulfinyl or C_1-C_6 alkylsulfonyl groups;

R^2 is selected from the group consisting of hydrogen, a straight-chain or branched, saturated or unsaturated alkyl chain having 1-20 carbon atoms, which is unsubstituted or substituted at least once by halogen, C_1-C_6 alkoxy, C_1-C_6 alkylmercapto, C_1-C_6 alkoxycarbonyl or C_1-C_6 alkylsulfonyl groups;

R^3 is selected from the group consisting of hydrogen, hydroxy and halogen;

R^4 is selected from the group consisting of hydrogen and hydroxy;

R^5 is selected from the group consisting of hydrogen, hydroxy and halogen;

R^6 is halogen;

X is selected from the group consisting of a valence bond, an oxygen atom, a sulfur atom, a sulfinyl group and a sulfonyl group;

Y is selected from the group consisting of a valence bond, an oxygen atom and a sulfur atom;

n is an integer of 1, 2 or 3;

with the proviso that at least one of the residues R^3 or R^5 is hydrogen and that, furthermore, R^3 and R^4 can signify a further bond between C-2' and C-3', whereby the amino group of the nucleoside base may be unsubstituted or substituted by a known amino protecting group,
their tautomers, their optically active forms and racemic mixtures, and their physiologically acceptable salts of inorganic and organic acids or bases.

2. The nucleotide derivative according to claim 1, wherein R^1 is a straight-chain C_8-C_{15} alkyl group, which is unsubstituted or substituted by a C_1-C_6 alkoxy or a C_1-C_6 alkylmercapto group.

3. The nucleotide derivative according to claim 1, wherein R^2 represents a straight-chain C_8-C_{15} alkyl group, which is unsubstituted or substituted by a C_1-C_6 alkoxy or a C_1-C_6 alkylmercapto group.

4. The nucleotide derivative according to claim 1, wherein X is sulfur, sulfinyl or sulfonyl, and Y is oxygen.

5. The nucleotide derivative according to claim 1, wherein X and Y are valence bonds, R^2 is hydrogen, and R^1 is a C_1-C_{20} alkyl group, which is unsubstituted or substituted by a C_1-C_6 alkoxy or a C_1-C_6 alkylmercapto group.

6. The nucleotide derivative according to claims 1 to 6, wherein n is 1.

7. The nucleotide derivative according to claims 1 to 6, wherein R^5 is selected from the group consisting of hydrogen, and halogen.

8. The nucleotide derivative according to claim 1, wherein R^3 and R^4 are individually selected from the group consisting of hydroxy or a hydrogen atom.

9. The nucleotide derivative according to claim 1, wherein R^5 is hydrogen.

10. The nucleotide derivative according to claim 1, wherein R^6 is fluoro.

11. The nucleotide derivative according to claim 1, wherein R^3 and R^4 signify a further bond between C-2' and C-3'.

12. The nucleotide derivative according to claim 1, wherein R^4 and R^5 are hydrogen.

13. The nucleotide derivative according to claim 12, wherein R^3 is hydroxy.

14. The nucleotide derivative according to claim 1, wherein

R^1 is a straight-chain C_9-C_{13} alkyl group which is unsubstituted or substituted by a methoxy, ethoxy, butoxy, hexyloxy, methylmercapto, ethylmercapto, propylmercapto, butylmercapto, or hexylmercapto residue;

R^2 is a straight-chain C_8-C_{12} alkyl group which is unsubstituted or substituted by a methoxy, ethoxy, butoxy, hexyloxy, methylmercapto, ethylmercapto, propylmercapto, butylmercapto, or hexylmercapto residue;

R3 is a hydroxy residue;

R4 is a hydrogen atom; and

R5 is a hydrogen atom.

15. The nucleotide derivative according to claim 1, wherein the nucleoside portion is
2-Chloro-9-(2'-deoxy-2'-fluoro arabinofuranosyl)adenine.

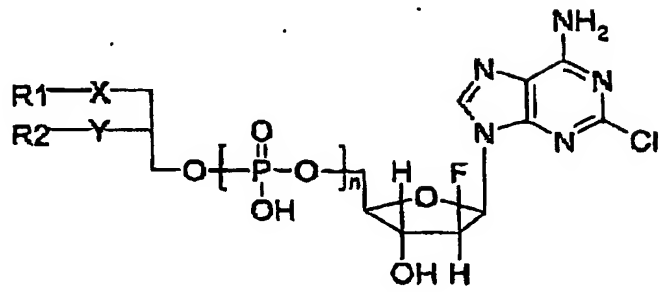
16. A composition comprising at least one compound according to claim 1 in combination with a pharmaceutically acceptable adjuvant or vehicle.

17. A method for treating malignant tumors comprising administering to a patient in need of such treatment an amount of the composition according to claim 16 effective to treat said tumors.

18. The method according to claim 17, wherein said tumor is selected from the group consisting of carcinomas, sarcomas or leukemias.

19. A method for treating malignant tumors comprising administering to a patient in need of such treatment an amount of the composition according to claim 16 effective to treat said tumors in fixed or free combination with other anticancer agents.

20. A nucleotide derivative of formula II



(II)

wherein

R^1 is selected from the group consisting of a straight-chain or branched, saturated or unsaturated alkyl chain having 1-20 carbon atoms, which is unsubstituted or substituted at least once by halogen, C_1-C_6 alkoxy, C_1-C_6 alkylmercapto, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkylsulfinyl or C_1-C_6 alkylsulfonyl groups;

R^2 is selected from the group consisting of hydrogen, a straight-chain or branched, saturated or unsaturated alkyl chain having 1-20 carbon atoms, which is unsubstituted or substituted at least once by halogen, C_1-C_6 alkoxy, C_1-C_6 alkylmercapto, C_1-C_6 alkoxycarbonyl or C_1-C_6 alkylsulfonyl groups;

X is selected from the group consisting of a valence bond, an oxygen atom, a sulfur atom, a sulfinyl group and a sulfonyl group;

Y is selected from the group consisting of a valence bond, an oxygen atom and a sulfur atom;

n is an integer of 1, 2 or 3;

whereby the amino group of the nucleoside base may be unsubstituted or substituted by a known amino protecting group,
their tautomers, their optically active forms and racemic mixtures, and their physiologically acceptable salts of inorganic and organic acids or bases.

21. The nucleotide derivative according to claim 20, wherein R^1 is a straight-chain C_8-C_{15} alkyl group, which is unsubstituted or substituted by a C_1-C_6 alkoxy or a C_1-C_6 alkylmercapto group.

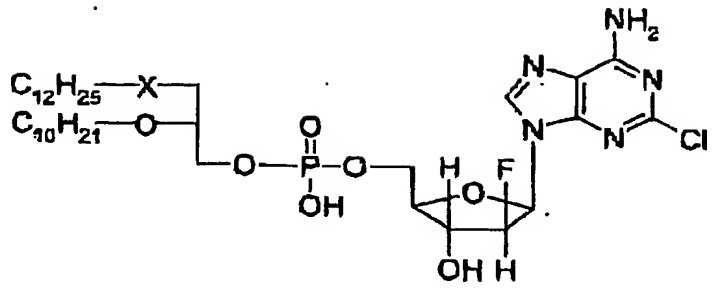
22. The nucleotide derivative according to claim 20, wherein R^2 represents a straight-chain C_8-C_{15} alkyl group, which is unsubstituted or substituted by a C_1-C_6 alkoxy or a C_1-C_6 alkylmercapto group.

23. The nucleotide derivative according to claim 20, wherein X is sulfur, sulfinyl or sulfonyl, and Y is oxygen.

24. The nucleotide derivative according to claim 1, wherein X and Y are valence bonds, R^2 is hydrogen, and R^1 is a C_1-C_{20} alkyl group, which is unsubstituted or substituted by a C_1-C_6 alkoxy or a C_1-C_6 alkylmercapto group.

25. The nucleotide derivative according to claims 1 to 6, wherein n is 1.

26. The nucleotide derivative according the claim 1 or 20, wherein the compound is:



wherein X is sulfur, sulfinyl or sulfonyl.

27. A composition comprising at least one compound according to claim 1 - 20 in combination with a pharmaceutically acceptable adjuvant or vehicle.

28. A method for treating malignant tumors comprising administering to a patient in need of such treatment an amount of the composition according to claim 28 effective to treat said tumors.

29. The method according to claim 29, wherein said tumor is selected from the group consisting of carcinomas, sarcomas or leukemias.

30. A method for treating malignant tumors comprising administering to a patient in need of such treatment an amount of the composition according to claim 29 effective to treat said tumors in fixed or free combination with other anticancer agents.

Abstract

The subject of the present invention are specific lipidesters of halogenated-adenine nucleotides and the use of such lipidesters in the treatment of tumors.

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